The New Generation of Meningococcal Conjugate Vaccines: Rationale and Global Potential

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The serogroup distribution of *Neisseria meningitidis* strains implicated in invasive disease varies geographically and temporally. Monovalent serogroup C conjugate vaccines have successfully reduced serogroup C disease in countries where they are used. However, combinations containing multiple serogroups are needed to fully address disease prevention. GlaxoSmithKline Biologicals' combined serogroups C, Y and *Haemophilus influenzae* type b conjugate vaccine (Hib-MenCY-TT) has been shown to be immunogenic and well tolerated in infants. The novel Hib-MenCY-TT vaccine has the potential to prevent approximately 90% of non-serogroup B disease in the US. Several manufacturers have investigated tetravalent ACWY conjugate vaccines. One ACWY conjugate vaccine has been licensed for use 2-55 year olds, but the immunogenicity in infants was reduced. Results of other ACWY vaccines using different protein conjugates have shown higher immunogenicity in infants. The next generation of combination meningococcal conjugate vaccines has potential to further reduce morbidity and mortality due to *N. meningitidis,* provided they are safe and immunogenic in infants and toddlers. A Hib-MenCY-TT vaccine could substantially reduce meningococcal disease in the US, while tetravalent ACWY conjugate vaccines have the potential to provide coverage across age strata against four of the five major serotypes implicated in invasive meningococcal disease.

Keywords: Meningitis, *Neisseria meningitidis*, vaccine, primary vaccination.

The first meningococcal serogroup C conjugate vaccines were deployed in the United Kingdom in 1999 in response to an increase in endemic meningococcal serogroup C disease that particularly affected adolescents. Between 1994 and 1999 deaths in adolescents due to serogroup C exceeded those due to serogroup B in the UK. By 1999 serogroup C was responsible for 34% of meningococcal infections in the UK, compared to 25.8% in 1994 (1). The effects of infant vaccination coupled with a large catch-up campaign targeting 12 month olds to 17 years olds was rapid and substantial, with reductions in disease incidence of more than 80% observed in most age groups within 18 months of implementation (2). Since then, serogroup C conjugate vaccines have been effectively introduced into routine vaccination schedules in some European countries such as Spain, Ireland, Belgium, the Netherlands and in Canada and Australia (3,4,5). The monovalent serogroup C vaccine has now been combined with Hib conjugate vaccine into a combination Hib-MenC-TT vaccine (*Menitorix*™, GlaxoSmithKline Biologicals, Belgium) that was approved for use by the UK Medicines and Healthcare Products Regulatory Agency in 2005 as a primary and booster vaccine. *Menitorix*™ has been used in the United Kingdom as a booster dose during the second year of life since September 2006.

Invasive meningococcal disease is a major cause of morbidity and mortality worldwide. Most disease cases are caused by five serogroups (A, B, C, W-135 and Y), of which four (A, C, W-135 and Y) are currently candidates for prevention by vaccination with polysaccharide-protein conjugate vaccines. The distribution of serogroups responsible for invasive meningococcal disease varies geographically and some variation with age is also apparent. Changing serogroup distribution over time may also occur, as observed during the last two decades with the emergence of serogroup Y as one of the three major pathogens, along with serogroups B and C, in the United States (6). It is this diversity and potential for temporal change in the epidemiology of invasive disease that has made development of 'global' tetravalent ACWY conjugate vaccines for use across a broad range of age groups so attractive for the prevention of meningococcal disease. In addition, "designer vaccines" could be developed to address specific medical needs in a given country, such as the recent emergence of serogroup Y in the US and Latin America (7,8).

In sub-Saharan Africa, Middle East, parts of Asia and Russia, serogroup A remains the major cause of endemic disease, as well as outbreaks and epidemics that continue to regularly devastate affected populations. Between the years 1995-2004, meningococcal outbreaks in Africa, largely due to serogroup A, caused 700,000 cases and 60,000 deaths (9). In contrast, serogroup A is of less importance in Europe, the United States, Latin America and Australia, where serogroups B and C (and Y in the United States, and with increasing frequency in Latin America) predominate (6,3).

The last two decades have seen changes in meningococcal serogroup distribution in both developed and developing countries. In Africa, serogroup W-135 has emerged as a growing threat, causing major outbreaks in Burkina Faso and Chad (9). In the Middle East, serogroup W-135 has also been observed as an important cause of outbreaks amongst pilgrims

in Saudi Arabia (6). In the United States the percentage of invasive meningococcal disease cases due to serogroup Y increased from approximately 2% before 1992 (6), to 35% in 2007 (10). The importance of serogroup Y may be changing in other countries, with increased serogroup Y disease previously observed in Sweden and Israel (6) and more recently in South America (11). Outside of the Americas, serogroup Y invasive disease has been reported in Finland, Latvia and Sweden (3). However, in most other countries, serogroups W-135 and serogroup Y make a lesser contribution to invasive disease cases to date.

Worldwide, the highest incidence rates of meningococcal disease are observed in infants and young children, with a secondary peak during adolescence/young adulthood. Between 15%-17% of all meningococcal disease cases occurred in children under 2 years of age in the United States between 2005 and 2007 (10). In Europe 1999-2006, between 11% and 17% of meningococcal disease cases occurred in children under one year of age (3).

Serogroup B, for which no vaccine candidate is currently available, causes substantial disease in infants and children: approximately 50% of meningococcal disease cases in children under 5 years of age in Europe and the US (3,10). Serogroup B along with serogroup C, is responsible for the majority of sporadic meningococcal disease cases in developed countries, and since 1991, has caused a protracted epidemic in New Zealand (6,11).

The contribution of serogroup C and Y disease appears to rise with increasing age (3, 10). In the United States it has been estimated that a combined conjugate vaccine formulation covering serogroups C and Y with effectiveness in both infants and adolescents could prevent up to 50% of meningococcal cases and 62% of deaths (7).

The varied and inconstant manner in which meningococcal serogroups are distributed means that larger combination vaccines containing several serogroups are needed to fully address meningococcal disease prevention. Introduction of combination vaccines into vaccination schedules has resulted in improved vaccine coverage, improved timeliness of vaccination, by providing multiple antigens in a single injection (12,13). The Netherlands experience showed that a mass vaccination campaign with the serogroup C conjugate vaccine in all individuals aged 1-20 years, followed by routine toddler vaccination, led to substantial herd immunity and protection of infants (14). However, catch-up campaigns with extensive coverage cannot be implemented in every country. Hence, new combined meningococcal vaccines should be immunogenic in infants in order to prevent disease in the population most at-risk.

GlaxoSmithKline Biologicals (GSK) has developed a combined conjugate vaccine targeting serogroups C, Y and combined with *Haemophilus influenzae* type b (Hib) conjugate vaccine (Hib-MenCY-TT). The Hib-MenCY-TT vaccine builds on *Menitorix*™, the first combination Hib-MenC-TT conjugate vaccine routinely used in the UK as a booster against Hib and *N. meningitidis* serogroup C in toddlers. Three priming doses of the novel Hib-MenCY-TT vaccine were shown to be immunogenic and well tolerated in infants when co-administered with routinely scheduled vaccines (15). The immune responses to the Hib and serogroups C components were similar to US-licensed (Hib) and Australian-licensed (Hib and MenC) control vaccines administered separately, and the immune responses to co-administered vaccine antigens were unaffected (15). Immune memory after priming with Hib-MenCY-TT was demonstrated after immunological challenge with serogroup C and Hib polysaccharides at 11-14 months of age. Further studies confirming the immunogenicity and tolerability of Hib-MenCY-TT are underway. This unique vaccine has the potential to prevent approximately 90% of non-serogroup B disease in the United States without adding extra injections to the US crowded vaccination schedule (10).

To date only one combined tetravalent ACWY conjugate vaccine has been licensed for use, although several more are in development. The licensed ACWY vaccine is conjugated to diphtheria toxoid, and is licensed in the US and Canada for individuals 2-55 years of age. However, in clinical trials in infants, the vaccine showed reduced immunogenicity as compared to the older age groups (6). An ACWY-CRM197 conjugate vaccine in development was shown to be immunogenic in infants (16). GlaxoSmithKline's experimental tetravalent ACWY vaccine conjugated to tetanus toxoid (ACWY-TT) was immunogenic and well tolerated in adolescents and young adults 15 to 25 years of age (17) and in children 3-5 years of age and toddlers 12-14 months of age (18).

Monovalent meningococcal serogroup C vaccines have delivered substantial reductions in meningococcal disease due to serogroup C. The next generation of combination meningococcal conjugate vaccines stands to further reduce morbidity and mortality due to *N. meningitidis,* provided they are safe and immunogenic in infants and toddlers. The novel Hib-MenCY-TT conjugate vaccine that specifically targets epidemiological needs of countries where serogroup Y is important, such as the US and possibly Latin America, has the potential to provide early protection for infants. The tetravalent ACWY conjugate vaccine could be utilized in all regions with a broad age indication for young children and adolescents against four of the five major serotypes implicated in invasive meningococcal disease.

References

1. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against

meningococcal serogroup C disease in the UK: a success story. Vaccine 2001;20 Suppl 1:S58-67.
2. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365-67.
3. European Union Invasive Bacterial Infections Surveillance Network. Invasive *Neisseria meningitidis* in Europe 2006 report.
4. Snape MD, Pollard AJ. Meningococcal polysaccharide-protein conjugate vaccines. Lancet Infect Dis 2005;5(1):21-30.
5. De Wals P, Deceuninck G, Boulianne N, De Serres G. Effectiveness of a mass immunization campaign using serogroup C meningococcal conjugate vaccine. JAMA 2004;292:2491-4.
6. Kimmel SR. Using the tetravalent meningococcal polysaccharide-protein conjugate vaccine in the prevention of meningococcal disease. Ther Clin Risk Manag 2008;4:739-45.
7. Lingappa JR, Rosenstein N, Zell ER, Shutt KA, Schuchat A, Perkins BA. Active Bacterial Core surveillance (ABCs) team. Surveillance for meningococcal disease and strategies for use of conjugate meningococcal vaccines in the United States.Vaccine 2001;19:4566-75.
8. Vázquez JA, Adab R, Brandileone MC, et al. Molecular characterization of invasive serogroup Y *Neisseria meningitidis* strains isolated in Latin America region. [abstract]. International Pathogenic Neisseria Conference. Rotterdam, The Netherlands.7-12 September 2008.
9. World Health Organization. Enhanced surveillance of epidemic meningococcal meningitis in Africa: a three-year experience. WER 2005;80:313-20.
10. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance. [accessed 06 March 2009]. Available at: http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm.
11. Sáfadi MA, Barros AP. Meningococcal conjugate vaccines: efficacy and new combinations. J Pediatr (Rio J). 2006 Jul;82(3 Suppl):S35-44.
12. Marshall GS, Happe LE, Lunacsek OE, et al. Use of combination vaccines is associated with improved coverage rates. Pediatr Infect Dis J 2007;26:496-500.
13. Kalies H, Grote V, Verstraeten T, Hessel L, Schmitt H-J, von Kries R. The use of combination vaccines has improved the timeliness of vaccination in children. Pediatr Infect Dis J 2006;25:507-12.
14. de Greeff SC, de Melker HE, Spanjaard L, Schouls LM, van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. Pediatr Infect Dis J 2006;25:79-80.
15. Nolan T, Lambert S, Roberton D, Marshall H, Richmond P, Streeton C, Poolman J, Boutriau D. A novel combined Haemophilus influenzae type b-*Neisseria meningitidis* serogroups C and Y-tetanus-toxoid conjugate vaccine is immunogenic and induces immune memory when co-administered with DTPa-HBV-IPV and conjugate pneumococcal vaccines in infants. Vaccine 2007;25:8487-99.
16. Snape MD, Perrett KP, Ford KJ, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. *JAMA* 2008;299:173-84.
17. Ostergaard L, Lebacq E, Poolman J, Maechler G, Boutriau D. Immunogenicity, reactogenicity and persistence of meningococcal A, C, W-135 and Y-tetanus toxoid candidate conjugate (MenACWY-TT) vaccine formulations in adolescents aged 15-25 years. *Vaccine* 2009;27:161-68.
18. Prieler A, Knuf M, Poolman J, Vink P, Boutriau D. Immunogenicity of 1 dose of a candidate meningococcal tetravalent tetanus toxoid conjugate (MenACWY-TT) vaccine in 12-14 month and 3-5 year olds [abstract]. ICAAC, 17-20 September 2006.